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Narrative review

Point-of-care testing for sexually transmitted infections in low-resource settings

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ABSTRACT

Background: Both the global incidence and the prevalence of sexually transmitted infections (STIs) continue to increase, affecting hundreds of millions of individuals, particularly in low-to middle-income countries. Although a definitive diagnosis is desirable to inform STI treatment, syndromic management is the most widely used strategy in resource-limited settings. With the development of point-of-care (POC) tests, it is important to discuss how laboratories will need to adapt to new training and supervisory roles in support of testing, which will largely be performed by peripheral clinical staff.
Objectives: To discuss potential applications of STI POC tests, how they could improve existing STI control strategies and the role of clinical and reference laboratories in support of initiatives to improve STI management and control activities.
Sources: Narrative literature review and expert opinion.
Content: The paper outlines the current status of the STI epidemic worldwide and discusses the problems associated with current approaches to control these infections, particularly in low-resource settings. The roles of clinical and reference laboratories will need to change to provide support for POC and near-patient STI testing as these technologies are introduced into clinical as well as laboratory settings.
Implications: Laboratories will be expected to play a leading role in the introduction and implementation of POC and near-patient STI testing. They will be required to facilitate training and provide technical and supervisory support to clinical staff on the use of these technologies to augment existing STI management and surveillance programmes. In order to provide quality service, they will need to develop, introduce and maintain sustainable local quality control and external quality assurance systems. Evidence from implementation research for introduction and scale up of STI POC tests in different STI epidemic and laboratory infrastructure settings is required. **S. Vargas, Clin Microbiol Infect 2022;28:946**

Background

The global incidence of sexually transmitted infections (STIs) remains high and is increasing [1]. The World Health Organization (WHO) has estimated that in 2016, there were 376 million new infections with one of four curable STIs: chlamydia (127 million), syphilis (6.3 million), trichomoniasis (156 million) and gonorrhoea (87 million), and another curable STI caused by *Mycoplasma genitalium* has frequently been detected in many settings [2,3]. Unfortunately, many of these infections are increasingly caused by pathogens that have acquired resistance to commonly used antimicrobial agents [4]. In addition, more than 500 million people are estimated to be living with viral STIs, notably genital herpes simplex virus infection, while approximately 300 million women have

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human papillomavirus infection, the primary cause of cervical cancer [1]. Both bacterial and viral infections are recognized to cause a high burden of morbidity and mortality, particularly in low- and middle-income countries, impacting the quality of life of adults and, as a result of vertical transmission, of infants and children. These 'conventional STIs' also facilitate the sexual transmission of human immunodeficiency virus (HIV) by increasing both the susceptibility to HIV infection and infectiousness of those persons who are already co-infected, because they elicit increased HIV shedding in genital inflammatory exudates and produce breaches in skin and mucous membranes [5,6].

Prompt and effective detection and treatment of STIs are considered essential components of STI control programmes in order to prevent development of sequelae and reduce subsequent spread of infection [7]. In high-resource settings, the classical role of the clinical laboratory in supporting STI programmes is to aid in the establishment of a definitive diagnosis in individual symptomatic cases of disease and their identified sexual contacts, using established, but often specialized, microscopic, cultural, serological and, more recently, nucleic acid amplification tests [8]. The ability to apply state-of-the-art diagnostic tests to achieve an aetiological diagnosis and thus pathogen-targeted treatment is accepted in most high-income settings. In addition, these techniques are often applied to non-invasive clinical specimens and have also been widely used to screen asymptomatic populations at increased risk of infection with STI pathogens [9].

However, in resource-constrained settings the cost of equipping and staffing such laboratory facilities at the hospital level, let alone in peripheral health centres, clinics or dispensaries, is prohibitive, and the vast majority of individual patients do not have access to sites with laboratory facilities or cannot afford to pay for laboratory investigations. Unfortunately, centralizing such facilities necessitates the development of transport networks to ensure timely submission of both specimens and return of results; this inevitably results in treatment delays and therefore missed opportunities for treatment as a result of loss to follow up [10,11].

It is not surprising, therefore, that alternative approaches have been sought to overcome these obstacles to quality care, including treatment based on a 'typical' clinical presentation ascertained by expert clinicians (presumptive clinical diagnosis) or based on knowledge of the patterns of causative organisms and their antimicrobial susceptibilities of certain clinically defined presentations, based on symptoms and signs, such as urethral discharge in men, vaginal discharge and genital ulcer disease (syndromic management). More recently, the development of point-of-care (POC) and near-patient diagnostics for STIs has resulted in vigorous debate among specialists, clinicians, primary health workers, laboratory technicians, public health experts and policy-makers regarding the appropriate use of these technological advances, particularly in resource-constrained settings [12,13].

Objectives

In this narrative literature review we discuss the possible applications of POC and near-patient diagnostic tests, how they could improve existing STI control strategies, particularly in low- and medium-resource settings, and the implications for the role of clinical and reference laboratories that support STI and control activities through STI testing.

Traditional approaches to STI diagnosis in resource-constrained settings

Classic strategies of STI diagnosis involve aetiological diagnosis and clinical diagnosis. Aetiological diagnosis refers to proper identification and/or isolation of the infectious agent, and requires full equipment, reagents, supplies and qualified personnel for performing all necessary assays [14]. Therefore, agent identification will be performed in the few sites equipped with proper infrastructure, such as reference or research laboratories. As results are often only available after several days, treatment is delayed and there is loss to follow up, increasing the chance of new transmissions or complications related to disease.

On the other hand, clinical diagnosis refers to the identification of signs and symptoms typically associated with a single, specific, infectious agent for which only specific treatment is given [14]. Similarities between the clinical presentations of various diseases that require different treatments, frequent infection with more than a single STI pathogen, plus atypical clinical presentations of diseases, have led to considerable mistreatment and undertreatment; however, clinical diagnosis continues to be widely-practiced in many low- and middle-income countries. With this last approach, treatment outcomes are almost totally dependent upon the skills of the examining clinician.

Syndromic management in resource-constrained settings

In general, syndromic management theoretically has the advantage of providing effective treatment on initial patient presentation at even remote clinical sites [15]. It is relatively inexpensive as few laboratory tests are routinely performed and standardized treatments (usually using polypharmacy) are provided. However, the effectiveness of the approach and therefore the treatments provided are dependent upon the quality of aetiological surveillance studies performed to determine patterns of infection within each syndrome. These comprehensive aetiological studies, using the most sophisticated laboratory techniques available to detect all possible causes, should be performed on a large series (100–200) of patients presenting with each defined syndrome, preferably at multiple sentinel sites. Using the data generated, standardized treatment algorithms (syndromic flowcharts) are designed to guide health-care workers in the management of patients for a particular syndrome in that geographical region [16]. The aetiological studies should be repeated periodically (preferably yearly or at least every 2 years) in order to detect changes in patterns of disease and their antimicrobial susceptibilities within the community and to inform any changes required to the syndromic flow charts.

WHO has advocated the adoption of syndromic management principles and published flow charts for a range of clinical 'syndromes' [16], but ideally these algorithms should be adapted to address local patterns of infection within each syndrome. Unfortunately, the WHO flowcharts have often been reproduced locally, without being informed by local data, with disappointing results. It is clear that while the approach works reasonably well in the management of men presenting with symptoms and signs of urethral discharge and initially in cases of genital ulcer disease in both men and women, changes in the aetiology of genital ulcer disease in many countries have resulted in the need to modify flowcharts to allow for the emergence of genital herpes as a major cause of genital ulcer disease with a decrease in the relative prevalence of chancroid caused by *Haemophilus ducreyi* [17–19].

The use of syndromic management approaches for the management of vaginal discharge has proved to be the most contentious, especially in societies with low STI prevalence rates. The automatic provision of treatment for gonococcal and chlamydial cervical infections (which are commonly asymptomatic) in women presenting with vaginal discharges, which are often caused solely by microorganisms that have not been sexually transmitted, has long been debated. Modifications to algorithms using added 'risk

assessments' for gonococcal/chlamydial infection have frequently been made, but the positive predictive value of coincidentally managing gonococcal and chlamydial cervical infections remains unacceptably low [13,20]. In addition, because contact notification activities should be linked to the detection of an STI, the use of syndromic management algorithms for the 'vaginal discharge syndrome' has, in some societies, resulted in increased risk of domestic violence as a consequence of notifying partners without definitively detecting an STI pathogen. Unfortunately, there are also other associated disadvantages to the approach. The most frequently cited is the inevitable over-treatment that occurs as a result of the use of polypharmacy in order to provide therapeutic cover for alternative aetiologies and possible mixed infections. The extra cost of use of multiple antimicrobial agents and the potential risk of promoting antimicrobial resistance among STI pathogens and the co-existing microbial flora have also been discussed at length [21].

It should also be noted that syndromic management principles should only be applied to patients presenting with clinically confirmed symptomatic disease. Syndromic management does not address the high burden of asymptomatic carriage of STI pathogens in both sexes, which can only be detected and treated as a result of targeted STI testing in high prevalence populations or persons at particular risk of infection.

In order to provide laboratory support for syndromic management in resource-poor settings, it is important that a national or regional reference laboratory has the technical capacity to perform a wide range of sensitive and specific laboratory tests to establish the potential infectious causes of a number of syndromes in different populations. These tests should include specialized microscopy, culture and antimicrobial susceptibility tests, laboratory-based serology and nucleic acid amplification tests. A list of the specific tests that have been used to determine the patterns of infection that may be seen among consecutive patients presenting with the three most common disease syndromes in many resource-poor settings are shown in Table 1. A detailed description of these tests can be found in the WHO STI Laboratory Manual, which is also available online [8]. It is clear that the ability to perform many of these expensive, complex and technically demanding tests is limited to high-income settings and only a few reference laboratories, including national public health, university research or centralized private clinical laboratories in less affluent countries. Personnel from these reference laboratories should, ideally, travel to appropriate clinical sites that are known to have a high patient load, assist in the collection and preservation of specimens to be transported to the reference laboratory and perform specialist microscopic tests on site. Such studies should ideally be conducted annually, but at least every 2 years and be funded by national or regional public health agencies directly or by multinational/international donor organizations.

Point-of-care and near-patient tests for STIs

In 2004, WHO recognized a need for the development of new POC tests for STIs that could be employed in both high-income and low-to middle-income countries. At that time, WHO also published the so-called ASSURED criteria, to describe the ideal characteristics to which any new STI POC test should aspire. The new POC tests should ideally be Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment -free and Delivered (accessible and

Table 1
Laboratory-based investigations that can be applied to consecutive series of patients with defined symptomatic disease presentations to obtain data for design of STI syndromic management algorithms (flowcharts)

Syndrome	Test performed	Notes
Urethral discharge	Light microscopy	Gram-stained smear of urethral exudate for confirmation of urethritis
	Culture of endourethral swab for *Neisseria gonorrhoeae* on selective medium	To detect and confirm *N. gonorrhoeae* infection and test for antimicrobial susceptibilities
	NAAT on first catch urine or endourethral swab for *N. gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Trichomonas vaginalis*	PCR, TMA or other commercial multiplex NAAT test
	Syphilis serology	Both quantitative non-treponemal and confirmatory treponemal tests
	HIV serology	Screening test and, if positive, confirmatory testing
Vaginal discharge	Light microscopy	Gram-stained smear of high vaginal swab to detect bacterial vaginosis and budding yeasts
	Culture of endocervical swab for *N. gonorrhoeae* on selective medium	To detect and confirm *N. gonorrhoeae* infection and test for antimicrobial susceptibilities
	NAAT on first catch urine or endourethral swab for *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis*	PCR, TMA or other multiplex NAAT test
	Syphilis serology	Both quantitative non-treponemal and confirmatory treponemal tests
	HIV serology	Screening test and, if positive, confirmatory testing
Genital ulcer disease	Dark-field or direct immunofluorescence microscopy	To detect *Treponema pallidum* spirochaetes directly in ulcer exudates
	Light microscopy	Giemsa-stained smear of scrapings from edge of ulcer to detect 'Donovan bodies'
	Culture of swabs from ulcer base for herpes simplex virus	On susceptible tissue culture monolayers
	Culture of swab from ulcer base for *Haemophilus ducreyi* on selective medium	To detect and confirm *H. ducreyi* infection and test for antimicrobial susceptibilities
	NAAT on swab from ulcer base for *Treponema pallidum*, *H. ducreyi*, HSV1 and HSV2, *C. trachomatis*	Non-commercial multiplex PCR test for *Treponema pallidum*, *H. ducreyi* and HSV. Commercial PCR or TMA for *C. trachomatis*
	Chlamydial serology for lymphogranuloma venereum	Broadly cross-reactive, high titres indicative of lymphogranuloma venereum using the microimmunofluorescence test (titres $\geq$256)
	Syphilis serology	Both quantitative non-treponemal and confirmatory treponemal tests
	HIV serology	Screening test and, if positive, confirmatory testing

Abbreviations: HIV, human immuodeficiency virus; HSV, herpes simplex virus; NAAT, nucleic acid amplification test; TMA, transcription-mediated amplification.
Details of the tests are presented in a WHO manual, available online [8].

acceptable) to end users [19]. A number of POC or near-patient tests for syphilis, gonorrhoea, chlamydial infection, trichomoniasis, herpes and human papillomavirus have been developed and evaluated under both laboratory and field conditions, and many others are at various stages of development. Further details of these tests and descriptions of their development pipelines have been the subject of two recent publications [22,23]. Some of these are true POC tests, which can provide results within 30 minutes and patients can therefore wait for their results and, if necessary, receive treatment at that single clinic visit. Many of the existing immunochromatographic POC tests currently available to detect HIV or syphilis (treponemal) antibodies in finger-prick blood specimens have proved to be simple and rapid to perform, and are both sensitive and specific. Unfortunately, not all marketed tests for these two infections perform adequately in the field, and evaluation studies are required before countries purchase less-expensive, non-validated tests. WHO has therefore issued a set of agreed target product profiles that can be used to guide developers of new tests and inform evaluators of acceptable product characteristics [24]. These guidelines are currently being updated.

Dual HIV/syphilis (treponemal) POC tests are currently being evaluated by WHO in both well-resourced and under-resourced settings, not only for their performance characteristics in peripheral sites, but also for their utility, including acceptability to both patients and test providers [25]. Reactive treponemal syphilis tests indicate both current and previous exposure to the disease, so there is an ongoing need for tests that give a better indication of active syphilis infection and therefore the need for therapeutic intervention. A dual non-treponemal/treponemal test has proved to be specific in both laboratory-based and clinic-based studies, but appears to lack non-treponemal sensitivity at low rapid plasma reagin (RPR) titres (<1:16) [26].

Although initial immunochromatographic POC tests for chlamydial, gonococcal and trichomonal infections based on detection of specific antigens proved to be specific, they lacked acceptable levels of sensitivity [27]. The subsequent generation of tests, based on various amplified molecular technologies, have proved to have equivalent performance characteristics to those of laboratory-based molecular tests [13]. Unfortunately, they tend to have longer run times (up to 2 hours) and are relatively expensive, more technically complex and instrument-dependent. These tests have generally been classified as 'near-patient tests' that can be deployed at peripheral sites with meagre laboratory facilities and may require patients to return later for their results.

However, various companies are applying innovative technologies to reduce the time to results, the dependence upon mains electricity, the need for bulky complex and expensive instrumentation and the ability to detect multiple analytes simultaneously (multiplexing) associated with using less invasive clinical specimens such as urine and self-collected vaginal swabs (*N. gonorrheae*/*C. trachomatis*/*T. vaginalis*/*Mycoplasma genitalium*) and swabs from genital ulcerations (*Treponema pallidum*/*H. ducreyi*/herpes simplex virus 1 and 2) [13,22,23].

When they are deployed, these new tests, in common with tests for other infectious diseases, should be integrated seamlessly into existing clinical practice in the tiered health-care services in such a way as not to overburden already busy primary health-care workers while improving the detection and management of STIs [28]. As tests are validated and deployed in the health-care system, it is important to establish the use of each test within existing clinical guidelines to enhance patient care.

For example, should single syphilis and HIV or dual syphilis/HIV POC testing be routinely offered to women attending antenatal clinics, to patients presenting with symptoms of an STI, or offered to asymptomatic individuals who are perceived to be at increased risk of infection? For simple, inexpensive immunochromatographic tests such as treponemal syphilis and HIV POC tests, the policy should, ideally, be initiated across the entire health-care system—whether individuals present at a university teaching hospital or at a remote rural clinic. The finding of reactive tests could result in either direct intervention, or perhaps lead to the use of confirmatory POC or laboratory-based testing before treatment. In the case of more complex tests, such as multiplex molecular amplification testing for *Neisseria gonorrhoeae*/*Chlamydia trachomatis*/*Trichomonas vaginalis*, the test platforms should ideally be distributed across the health-care system bearing in mind budget constraints, facility requirements such as space, provision of electricity supply and staffing levels. The recent distribution of the Cepheid GeneXpert instruments having flexible module configurations by some national programmes for the diagnosis of tuberculosis and the detection of rifampicin-resistance in *Mycobacterium tuberculosis* could be used as a model for the roll-out of new STI POC tests [29].

Implications for the role of the laboratory in an era of increased STI POC testing

Laboratory professionals have long been involved in the whole process of STI diagnosis. They have been involved in all aspects of pre-analytical (sample collection, secure transportation, registration and processing), analytical (proper analysis and results reporting) and post-analytical (result registration and archival) phases of laboratory testing, independent of the level of complexity of the laboratory. With increased numbers of POC and near-patient tests being performed in non-laboratory settings, it is clear that the role of clinical, public health and reference laboratories will change. Depending on circumstances, the demand for simple laboratory-based testing for STIs should decrease, while the demand for confirmatory testing will be maintained or could increase. In addition, as POC and near-patient tests become less expensive, more portable and more user-friendly, they will be used extensively for surveillance, in screening programmes, in conjunction with syndromic flow charts to improve their specificity as well as use as primary diagnostic tests. While this may be initially perceived as a threat to the relative importance of the laboratory in the overall health-care system, there will be additional demands made on laboratory personnel, particularly in reference laboratories, in support of clinic-based testing. These include:

1) Sensitization and introductory training of all health workers (laboratory and non-laboratory) in the importance of introduction and use of STI POC tests in non-laboratory settings within the health-care system and defining the roles of all cadres of health workers to ensure success of the POCT roll-out.
2) Hands-on training of primary health-care workers on adequate specimen collection, the need for strict adherence to manufacturers' instructions for each test introduced and the need for scrupulous recording of test results in patient records and clinic registers. Where applicable, information should be entered on electronic databases for monitoring and evaluation purposes.
3) Perform training to ensure theoretical knowledge and proficiency of laboratory workers in clinical and reference laboratories in performing the STI POC tests being introduced and the reference/confirmatory tests that will be required to support the roll-out.
4) Preparation and distribution of External Quality Assurance specimens to clinical sites twice yearly using dried blood specimens [30], or dried tube specimens [31] or simulated swab specimens.

5) Take responsibility for the quality of STI POC testing at the clinical sites by making routine, periodic visits to the clinical sites, observing testing of known positive and negative samples, include re-testing of samples for evaluating consistency of results reported by clinical sites, inspecting clinic registers, discussing the results of External Quality Assurance testing and taking remedial action if necessary.
6) Writing 6-monthly progress reports during the first 18 or 24 months following STI POCT introduction to inform authorities of the benefits and disadvantages of POCT implementation and to identify issues that require remedial action.
7) Maintain and expand the scope and variety of laboratory tests that can be used to aid establishment of an aetiological diagnosis of individual cases (particularly in treatment failures) including performance of antimicrobial susceptibility testing for *N. gonorrhoeae*.
8) Perform systematic laboratory testing (as described above) on consecutive patients with defined clinical presentations to support and inform development of and changes to syndromic algorithms.
9) Perform laboratory/clinical studies to determine the performance characteristics and utility of new STI POC tests, and implement protocols for validation of off-label testing that could be introduced using laboratory-based tests as comparators.
10) Collaborate with clinical colleagues to determine the burden of STIs in asymptomatic individuals in general populations and those perceived to be at increased risk in order to determine the value of introduction of screening programmes using STI POC tests.

Concluding remarks

Overall, in low-to middle-income settings, it is anticipated that the role of peripheral clinical laboratories to provide primary testing for STI pathogens will decrease as more POC and near-patient testing is performed at clinical sites. However, their role in maintaining adequate diagnostic supplies, technical support for quality assurance and quality control activities will increase. Moreover, the responsibilities of reference laboratories should increase to include all the functions (1–10) listed above, including distribution of POC tests to clinical laboratories and acting as a liaison with diagnostics companies to ensure continuity of supplies and equipment maintenance.

Transparency declaration

IT, RB and KB alone are responsible for the views expressed in this publication and do not necessarily represent the decisions or the policies of the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction or the World Health Organization.

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Authors' contributions

RB and IT were responsible for the concept of this manuscript. RB and SV wrote the initial draft of the manuscript. GC, JQ, FV, IT, KB and IT reviewed and edited the manuscript. SV, GC, JQ, FV and KB performed the literature search. All the authors contributed to the design and critical revision of the manuscript.

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